REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow. Applicants and their attorneys and licensee would like to thank Examiner Epps-Ford for kindly granting an interview on May 31, 2006. During the interview, applicants discussed the issues that formed the basis of the Examiner rejections under 35 U.S.C. §112, first paragraph in regard to lack of written description and lack of enablement and also 35 U.S.C. §112, second paragraph. Applicants presented representative draft claims for discussion purposes to further define the N-terminal region of the MARCKS protein as beginning from the N-terminal glycine of SEQ ID NO:3, which applicants have amended to SEQ ID NO:4 because this latter sequence is to the amino acids sequence. The Examiner agreed that she would reconsider Dr. Indu Parikh's declaration and the data provided therein. Applicants also stated that they intended to provide a further declaration by Dr. Duncan Rogers who is the author of two scientific publications that the Examiner relied upon to support her lack of enablement and lack of written description rejections. The Examiner provided applicants with the impression that if the claim amendments as discussed were made and Dr. Rogers' declaration provided, the Examiner would reconsider Dr. Parikh's declaration and favorably consider the new claims.

Claims 77, 81, 83, 84, 90, 94, and 98, have been cancelled in this response without prejudice or disclaimer. Applicants reserve the right to file any unclaimed subject matter in one or more continuing applications. Claims 78, 85-87, 91, 95, 100-103, 106 and 110 are currently amended. Claims 111-115 have been added. This amendment is fully supported by the originally-filed application and original claims 2, 3, 4, 41, 49 and 50.

Claims 78, 85, and 91 have been amended to clearly identify the N-terminus of the claimed peptide fragments by reciting that the myristoylated peptide fragments begin at the N-terminal glycine of SEQ ID NO: 4. This sequence is the protein or amino acid sequence and is referenced in the claims rather than the cDNA sequence which is disclosed in SEQ ID NO:3. Applicants submit that this claim language is supported by original claim 49, the specification and by known properties of myristoylated proteins, the latter of which will be supported by the enclosed Attachments. Support for this amendment is found on page 12, lines 8-15 of the

present specification, where the fragments of the present invention are a "myristoylated peptide fragment of the N-terminal region of MARCKS protein," which is the proposed site of the protein's attachment to granule membranes. The specification also discloses on page 21, line 28 to page 22, line 4, an active peptide fragment of MARCKS protein, the MANS peptide which stands for myristoylated N-terminal sequence, as a 24-amino acid peptide (SEQ ID NO:1) beginning with myristic acid- G(glycine). The present application further discloses on page 22, line 29 to page 23, line 5, two publications disclosing the human MARCKS cDNA and amino acid sequences as provided in the sequence listing in SEQ ID NOS: 3 and 5 (cDNA sequence) and SEQ ID NOS: 4 and 6 (amino acid sequence), respectively. The protein or amino acid sequences are the same for the first 50 amino acids in both SEQ ID NOS: 4 and 6 with only two nucleotides different between the two disclosed proteins. The MARCKS protein amino acid sequence begins with a Met in SEQ ID NOS: 4 and 6.

The claimed myristoylated peptide fragments of the present invention begin at the N-terminal glycine residue of the MARKCS protein as exemplified by the MANS peptide. But it was known prior to the filing of the priority document of the present patent application, that eukaryotic proteins, and specifically MARCKS protein, were post-translationally myristoylated by replacing the initiation methionine at the N-terminus with a myristic acid which results in the myristic acid directly attaching to an N-terminal glycine. In support of this argument, applicants submit that it was known by persons skilled in the art that myristoyl CoA:protein N-myristoyltransferase (NMT) catalyzes the addition of myristic acid to the amino terminal glycine residues of a number of eukaryotic proteins. See Towler *et al.* (Attachment A), particularly the abstract and the first two paragraphs on page 2708. Additionally see page 2710, 1st column, under heading "Highly Purified NMT Does Not Possess an Intrinsic Methionine Aminopeptidase Activity," where it is disclosed "that the myristoylated glycine is immediately preceded by the initiator methionine residue. Thus, this methionine must be removed prior to myristoylation."

Also enclosed is a copy of a 1998 publication by Vergeres *et al.*, (See Attachment B) which discloses on page 5, bottom of column 1, that "the N-terminal glycine residue of MARCKS proteins is myristoylated via a reaction catalyzed by myristoyl CoA:protein N-myristoyl transferase (NMT) [3]. Studies with acylated peptides as well as with the intact protein

show that the myristoyl group is involved in membrane binding [8, 14-16]." Thus, applicants submit that the specification discloses active myristoylated peptide fragments of the N-terminal region of MARCKS protein, which is the proposed site of the protein's attachment to granule membranes. Towler *et al.* and Vergeres *et al.* provide evidence of mechanism by which the methionine is replaced which a myristic acid that links to the N-terminal glycine. Vergeres *et al.* further discloses that the myristoyl group is involved in membrane binding. Therefore, amended claims 78, 85 and 91 are supported and do not introduce any new matter.

Claims 87 and 103 and new claims 111 and 112 are supported by the specification on pages 2, lines 6-13 and 17, lines 1-20. Amended claims 100, 106 and 110 are supported by the specification on page 21, line 29-32. New claims 113-115 are supported by the specification on page 9, lines 31-33.

A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier. After amending the claims as set forth above, claims 78-80, 82, 85-89, 91-93, 95-97 and 99-115 are now pending in this application. No new matter has been added. Applicants acknowledge the withdrawal of the rejections of claims 1-4 and 6 based on obviousness grounds and all claims on the grounds of obvious-type double patenting.

1. <u>The presently claimed invention is supported by the written description</u>

Claims 77-110 are rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement because the Examiner states that applicants were not in possession of the full scope of invention. The Examiner states that the claims encompass peptides which are subsequences of the N-terminal sequence of SEQ ID NO:3 (MARCKS protein) and that the specification lacks sufficient guidance to select the subsequences that share the function of inhibiting mucus secretion dependent signaling. The Examiner also states that the specification lacks any working examples of any functional subsequences. Additionally, the Examiner has discounted the evidence of such active fragments that fall within the scope of the claims as provided in the Parikh Declaration submitted with the

previous response on September 6, 2005 because she considered the tested peptides to not be commensurate in scope with the breadth of the claims.

In response to this rejection, applicants have amended the claims to more clearly define their invention. Independent amended claims 78, 85 and 91 clearly define that the myristoylated peptide fragment consists of from about 10 to about 50 contiguous amino acids from the N-terminal glycine residue of the MARCKS protein as shown in SEQ ID NO: 4 and further recites that the peptide inhibits MARCKS protein-related mucus hypersecretion. This language defines that the claimed peptides begin at the N-terminal glycine and range from about 10 contiguous amino acids up to about 50 contiguous amino acids of MARCKS protein as defined by SEQ ID NO:4. All of the dependent claims from these three independent claims contain this same feature.

As discussed at the Examiner interview, the amended claim language makes it clear which peptide fragments are encompassed by the invention. In view of these amended claims, it is requested that the Examiner reconsider Dr. Indu Parikh's declaration submitted with the previous response on September 6, 2005, to support applicants' position that the claimed peptides are active in inhibiting mucus hypersecretion. Applicants submit that the data shows that myristoylated peptides that begin with the N-terminal glycine are representative of the active peptide fragments as sufficiently disclosed in the application. Applicants have not resubmitted this declaration and its exhibits but request that the Examiner review this declaration which is already of record along with these arguments and amended claims. To reiterate, applicants submit that Dr. Parikh's declaration provides data showing that MANS peptide (BIO124) and other peptides of varying length from the N-terminal glycine of the MARCKS protein, i.e., 1-10, 1-12, 1-16 and 1-20 amino acids, inhibit mucus hypersecretion in the well-established ovalbumin-sensitized mouse model of asthma. Dr. Parikh's declaration cites a 1995 publication by Eum *et al.* that supports that this model was well known and used by persons skilled in the field prior to the filing date of the present invention's priority document. This data supports applicants' position that no further experimentation was required to identify the full scope of the active peptide fragments encompassed by the pending claims. It is respectfully requested that the Examiner reconsider Dr. Parikh's declaration and its data and withdraw the lack of written description rejection of all of the claims.

In particular, it is unclear how claims 95, 101 and 107 and their dependent claims with the exception of claims 100, 106 and 110 are rejected based on these grounds. These latter claims have been amended to specifically define the MANS peptide as disclosed in the specification, on page 21, lines 29-32. Claims 95, 101 and 107 are directed to methods of administration of and formulations containing the defined MANS peptide.

Applicants submit all of the claims comply with the written description requirement, and that the specification describes the invention in sufficient detail that a person skilled in the art could conclude that the present inventors had possession of the claimed invention. The claimed methods utilize structurally defined peptides which possess specific functional activity. Although experimentation may be necessary to determine the amount of the peptides to administer to a cell, such experimentation is not undue, as the parameter of mucus inhibition can be measured by methods disclosed in the specification as in Examples 3 and 4, and by methods known to persons skilled in the art at the time of filing of the present application (see Eum *et al.* enclosed as Exhibit 2 of Dr. Parikh's declaration) as discussed above. Applicants submit that the specification does provide adequate written description in sufficient detail to one skilled in the art to practice the present invention without undue experimentation.

Applicants respectfully request that the Examiner reconsider this rejection based upon the arguments and supporting documents presented herein and pending claims, and withdrawn this rejection.

2. <u>The presently claimed invention is enabled for the full scope of the claimed invention</u>

Claims 77-110 are rejected under 35 U.S.C. § 112, first paragraph as allegedly not being enabled for the full scope of the claims. To support this rejection, the Examiner states that while she considers the specification enabling for inhibiting mucus secretion *in vitro* and for decreasing mucus secretion in a mouse model of asthma by the administration of the MANS peptide, she does not consider the specification enabling for the treatment of other diseases with the peptide as claimed in the previous set of claims.

As discussed above, claims 78, 85 and 91 have been amended to clearly define the active peptide fragments that are encompassed by the claims, and therefore, overcome any suggestion that undue experimentation is required to practice the present invention as claimed.

The Examiner cites two publications by Dr. Duncan Rogers (2003) and (2001) and a publication by Dr. Peter Barnes (2002) as allegedly supporting her position for lack of enablement on a number of issues, including but not limited to, that there is no guidance for inhibiting mucus hypersecretion while maintaining the normal levels of mucus in a patient and that the clinical benefits from inhibiting mucus hypersecretion are still not certain which then casts doubts on this therapeutic approach to treat mucus hypersecretion.

In response to these allegations that the Examiner suggests is supported by these publications, applicants herewith submit a declaration under 37 C.F.R. § 1.132 made by Dr. Duncan Rogers (See Attachment C), the author of two of the publications cited by the Examiner and a colleague of Dr. Barnes. Dr. Rogers read the Office Action of December 7, 2005 and the Examiner's arguments that are allegedly supported by his and Dr. Barnes' publications, and on that basis provides his declaration. It is requested that the Examiner review this enclosed declaration and consider its content in support of applicants' position.

Briefly in paragraph 3 of his declaration, Dr. Rogers places his 2001 publication in context and he provides an explanation of the data over a period of years. Dr. Rogers then comments that based upon experiments that were performed by skilled scientists in the pulmonary field or from the review of scientific publications authored by such scientists that such evidence does support that the inhibition of excessive mucus hypersecretion does alleviate some or all of the symptoms which are known to characterize respiratory diseases. Dr. Rogers then references publications including several national publications, such as guides and summaries, (Exhibits 2-4), some of which have been updated recently, which show that mucus plugging is a cause of airway obstruction and airflow is limited (See Exhibit 2, page 4 of Attachment C) and the recommendation to use mucolytic therapy to treat mucus hypersecretion in COPD (See Exhibit 3, page 24 of Attachment C) and how that recommendation has been

recent as opposed to about five years ago (See Exhibit 4 of Attachment C). Only relevant portions of Exhibits 2 and 3 are provided with Dr. Rogers' declaration.

Additionally, Dr. Rogers references another of his publications from 2004 (Exhibit 5) in which he discusses the importance of treating airway mucus hypersecretion in asthma and how it has characteristic pathophysiological features. Mucus hypersecretion is known to be common to other hypersecretory respiratory diseases, such as COPD and cystic fibrosis (see page 241). Dr. Rogers' publication in Figure 8 on page 247 and Table 3 on page 248 disclose blocking mucus hypersecretion with mucolytic agents and that MARCKS inhibitors, such as MANS peptide, is a potential therapeutic inhibitor of mucin exocytosis. On page 4 of Dr. Rogers' declaration, first complete paragraph, he views the inhibition of airway mucus hypersecretion as a valid therapeutic target in both COPD and asthma, and particularly view anti-MARCKS therapy as a logical approach to reducing airway mucus hypersecretion. Along this same line of reasoning, Dr. Rogers than notes that the Barnes 2002 publication cited by the Examiner also identified MARCKS inhibitors as potential treatment for the airway mucus hypersecretion in COPD. Dr. Rogers further notes that his own 2003 publication cited by the Examiner, his 2004 publication (Exhibit 5) and Dr. Barnes 2002 publication cited by the Examiner cite Li *et al.* (Exhibit 6) which is a publication by the present inventors as evidence that anti-MARCKS therapy to inhibit airway mucus hypersecretion merits consideration for treatment. Similarly a subsequent publication by Dr. Adler's group, Singer *et al.* (Exhibit 7) extends this work and shows that MANS peptide inhibits mucus secretion in the mouse model of asthma which confirms that Drs. Rogers and Barnes were correct in supporting the role of anti-MARCKS therapy as a viable treatment to inhibit airway mucus hypersecretion. Finally, as a recent publication by Drs. Rogers and Barnes (Exhibit 8) confirms that the treatment of airway mucus hypersecretion is important in a number of severe respiratory conditions, including asthma, COPD and cystic fibrosis. This latter publication further confirms that both of these experts in the pulmonary disease field recognize the role of MARCKS protein in airway mucus hypersecretion and how anti-MARCKS therapy merits consideration in a treatment plan of pulmonary and respiratory diseases characterized by mucus hypersecretion.

Additionally, in paragraph 4 of Dr. Rogers' declaration, he addresses the Examiner's basis for lack of both written description and enablement for lack of guidance to maintain normal mucus secretion while inhibiting mucus hypersecretion. In this regard, Dr. Rogers states that one skilled in the art would be able to determine this level of inhibition of mucus hypersecretion without undue experimentation during clinical trials, and adjust the dosage accordingly.

Generally, applicants submit that Dr. Rogers' declaration has addressed and countered the basis upon which the Examiner used to rely on Rogers (2001) and (2003) publications and Barnes (2002) publication. Dr. Rogers states in his declaration in the beginning of paragraph 3, page 2, that he does not agree with the Examiner's characterization of portions of his and Dr. Barnes' publications. Therefore, in view of the favorable declaration by Dr. Rogers supportive of applicants' invention from the author of publications that the Examiner has cited in support of her rejections, it is requested that the Examiner consider Dr. Rogers' declaration and it supporting exhibits and withdraw the rejections on lack of enablement.

The Examiner also has stated that there is no evidence that the observed reduction in mucus secretion actually correlates to the alleviation of symptoms which the Examiner has based on the statements in the Rogers' and Barnes' publications. As noted above, Dr. Rogers states that his and Dr. Barnes' publications should not be interpreted as supporting the Examiner's position which he backs up with arguments and supporting documents. Particularly, in the paragraph bridging pages 2 and 3 of his declaration, Dr. Rogers generally the evidence from publications support that inhibition of excessive mucus secretion or hypersecretion does result in the alleviation of some or all symptoms of respiratory diseases.

Applicants submit that the data provided in Dr. Parikh's declaration on mucus hypersecretion inhibition and the data provided in Singer *et al.* (Exhibit 7 of Dr. Rogers' declaration) to show the effectiveness of the MANS peptide or active fragments in the well-accepted mouse model of asthma with its measurements of tissue after the animals are sacrificed is a well accepted method to measure mucus hypersecretion inhibition. Additionally, Dr Adler and a group of researchers have shown that the administration of MANS peptide improves airway function and that that symptom of pulmonary disease is related to mucus hypersecretion

in the mouse model of asthma. See Attachment D of an abstract presented at the International Conference of the American Thoracic Society, May 19-24, 2006 San Diego, California, and the abstract is referenced as "Proceedings of the American Thoracic Society, Vol. 3, page A713, 2006. The complete publication is presently under review by the Journal of Applied Physiology.

Therefore, in view of all of the arguments provided above, in view of Dr. Rogers' declaration and supporting exhibits and Dr. Parikh's declaration, and the abstract that provides evidence showing reduction in symptoms associated with pulmonary disease characterized by mucus hypersecretion, it is respectfully requested that the Examiner withdraw the lack of enablement rejection of all of the pending claims

3. Rejection based on Indefiniteness

Claims 77-90 and 95-106 are rejected for being definite because the claims recite a method of treating mucus secretion in the preamble of the claim whereas the language "whereby mucus hypersecretion" is recited in the body of the claim. Applicants have amended the preamble of the claims to recite that the methods are intended to inhibit mucus hypersecretion. In view of these amendments to the claims, it is requested that this rejection be withdrawn.

CONCLUSION

In view of the remarks and supporting documents presented herein and the information provided at the interview with the Examiner, Applicants respectfully submit that the claims define patentable subject matter. If, in the opinion of the Examiner, a telephonic conference would expedite the examination of this matter, the Examiner is invited to call the undersigned attorney at (919) 854-1400.

It is not believed that an extension of time and/or additional fee(s)-including fees for net addition of claims-are required, beyond those that may otherwise be provided for in documents accompanying this paper. In the event, however, that an extension of time is necessary to allow consideration of this paper, such an extension is hereby petitioned under 37 C.F.R. §1.136(a). Any additional fees believed to be due in connection with this paper may be charged to our Deposit Account No. 50-0220.

Respectfully submitted,

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